UNIVERSITI PUTRA MALAYSIA

DEVELOPMENT OF TAPERED OPTICAL FIBER-BASED SENSOR FOR DETECTION OF DENGUE II E PROTEINS

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

April 2018

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Doctor of Philosophy

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April 2018

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The escalating cases of dengue around the globe has become a major public health concern with an estimation of 300 million infections, annually. Due to the absence of a cure and a narrow time window for successful detection, survival relies heavily on sensitive, reliable, rapid and accurate diagnostics that would facilitate better clinical management and control over the epidemic. The underlying problem in managing the disease heightens when conventional diagnostics that are available today have crucial set-backs impeding efficient surveillance of the disease. For the past decade, tapered single-mode fibers have exhibited versatility and enticing sensitivity towards changes of its surrounding refractive index, making it favorable to be employed in sensing systems. The research work demonstrates the development of label-free tapered optical fiber-based sensor for the detection of dengue II E proteins. The sensing principle lies within the reaction of evanescent waves driven from the tapering of the optical fiber, towards changes within the external surrounding, in which would produce measurable response that enables to determine the concentration of the proteins. To ensure its selectivity, dengue II E protein complimentary antibodies were immobilized onto the surface of the tapered fiber. The proposed setup obtained a comparable sensitivity of 5.44 nm/nM with a detection limit of 1 pM within a short response time. For further performance enhancement of the sensing system, graphene oxide (GO) and polyamidoamine (PAMAM) dendrimer were integrated to promote higher surface to volume ratio, homogenous adhesion and better molecular orientation. The characteristics of these two nanomaterials are expected to increase the sensitivity of the sensor and its affinity towards dengue II E proteins. With both nanomaterials tested individually as enhancement layers onto the tapered fiber, better sensitivity was obtained when compared to the sensitivity obtained before, with values for PAMAM and GO at 19.53 nm/nM and 12.77 nm/nM, respectively. However, when both layers were applied onto the same tapered fiber, the performance of the sensor was not as satisfactory as PAMAM alone, as it only managed to achieve a sensitivity

value of 13.25 nm/nM. Noting that optical fibers are inexpensive, flexible, and now has shown promising performance in the detection of the dengue virus, it is anticipated of this work to be the first vital steps towards the development of better dengue diagnostics.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PEMBANGUNAN SENSOR BERPANDUKAN GENTIAN OPTIK TIRUS UNTUK PENGESANAN PROTEIN DENGGI II E

Oleh

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Kes-kes denggi terlonjak meningkat serata dunia mengakibatkan 300 juta jangkitan setiap tahun telah menjadi satu kebimbangan kesihatan yang utama. Disebabkan ketiadaan penawar, kemandirian bergantung khusus pada kaedah diagnostik yang sensitif, tepat dan mudah untuk dikendalikan. Masalah dalam menguruskan wabak ini memuncak apabila diagnostik lazim yang ada pada hari ini didapati gagal untuk memastikan pemantauan yang cekap. Untuk beberapa dekad yang lalu, gentian optik tirus telah menunjukkan kebolehan dan kepekaan terhadap perubahan indeks biasan didalam medium menyebabkan penggalakan untuk diterapkan dalam mekanisma sistem deria. Kerja penyelidikan ini memperagakan kemajuan sistem deria berasaskan gentian optik tirus tanpa penanda untuk pengesanan protein Denggi II E. Prinsip pengesanan tersebut terletak pada reaksi gelombang evanesent didorongi daripada proses penirusan gentian optik. Perubahan pada sekeliling gentian optik tersebut akan menghasilkan respon yang boleh diukur untuk mengenalpasti kepekatan protein. Untuk memastikan daya pengesanannya, pelengkap antibodi protein Denggi II akan diterapkan ke atas permukaan gentian optik tirus. Keputusan yg diperoleh menyatakan nilai sensitiviti setinggi 5.02 nm/nM dengan had pengesanan 1 pM dalam tempoh masa 15 minit. Untuk meningkatkan daya pengesanan sistem deria dengan selanjutnya, kajian diteruskan dengan penerapan Grafin oksida (GO) dan dendrimer Polyamidoamine (PAMAM) sebagai lapisan aktif diatas permukaan gentian optik tirus. Ciri-ciri kedua-dua nanomaterial tersebut adalah dijangka untuk meningkatkan kepekaan sensor tersebut dan daya afiniti ke arah protein Dengi II E. Dengan menguji kedua-dua nanomaterial secara berasingan sebagai lapisan aktif ke atas gentian tirus tersebut, daya pengesanan yang lebih baik dapat diperoleh berbanding dengan yang diperoleh tanpa lapisan aktif, dimana nilai sensitiviti PAMAM dan GO ialah 19.53 nm/nM dan 12.77 nm/nM masing-masing. Walaubagaimanapun, apabila kedua-dua lapisan diletak bersama, prestasi sensor tidak memberangsangkan dengan nilai sensitiviti 13.45nm/nM. Mengambil kira bahawa gentian optik adalah murah, anjal,

dan telah menunjukkan prestasi yang mempunyai harapan dalam pengesanan virus Denggi, kerja penyelidikan ini adalah dijangkakan sebagai langkah pertama yang penting ke arah kemajuan untuk diagnostik Denggi yang lebih berkualiti.

ACKNOWLEDGEMENTS

I would describe the whole PhD experience like a deep dive into the big blue ocean. There is a gazillion possibilities and opportunities to explore around you that the idea of it is exciting, yet in reality, without discipline, determination, passion, and the most important thing of all, perseverance, one may lose their way and drown into the abyss of fallen ambitions. Throughout these years, I would be lying if I say I did not have those detrimental moments where I almost drowned. But alhamdulillah, I am grateful that Allah has lend me strength to keep holding on, and also inspiring people who have never failed to encourage and motivate me to be the very best I can be and give my very best in whatever it is I do. Here, I would like to mention and thank some names whom without them, I would not have gotten to where I am now.

Firstly, my deep and sincere gratitude to my family, Ayah, Mama, and Aisyah, (plus my cats) for their continuous and unparalleled love, help, and support. They are the reason to everything I do, and the main cause to everything I have and will achieve.

To my main supervisor, Dr Hafiz, thank you for your endless guidance, patience, and valuable life lessons, "on and off the court". To my co-supervisor, Prof Adzir, I humbly thank you for the role-model image that you portray which consistently challenges and inspires me to achieve greater heights. Also to my co-supervisors, Dr Hanif and Dr Amir, thank you for the encouragement and help that you both have never failed to give. I would like to also express my appreciation to Mr. Zamili for his efficiency in making sure the lab is functioning at its best condition.

Aside from that, friends and colleagues helped a lot, too, especially in keeping me sane. To Syahirah, Syakirah, Elissa, and Rus, thank you for having my back all the time, regardless. To “budak comels”, Nad, for understanding my professional side so well, and Piji, for understanding my fun side, thank you for being you. You both have made the lab feel like home to me. To “Light girls”, it has been an awesome journey working alongside each and every one of you.

Last but not least, to Toriq, thank you for the simply, everything.

I guess the irony of a deep dive in the ocean is that, no matter how deep you thought you have dived, there will always be greater depths to discover. Yet, if you take a moment and look back at how you have gotten to where you are now, you cannot help but to smile a little and realize how amazing it has been, and it would not have been so without Allah’s will, and of course, these people. Thank you, again.

The thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

AFM	Atomic force microscope
APTES	(Aminopropyl) triethoxysilane
ASE	Amplified spontaneous emission
ASE	Amplified spontaneous emission
C-H	Methyl
DENV	Dengue virus
DHF	Dengue hemorrhagic fever
DSS	Dengue shock syndrome
C	Capsid
PrM	Protein membrane
NS	Non-structural protein
ELISA	Enzyme linked immunosorbent assay
PCR	Polymerase chain reaction
RT-PCR	Real-time polymerase chain reaction
LSPR	Long surface plasmon resonance
Ge	Germanium
SiO_2	Silicon oxide
HF	Hydrofluoric acid
CO_2	Carbon dioxide
LP_{01}	Fundamental mode
EDX	Energy-dispersive X-Ray
FESEM	Field emission scanning electron microscope
FSR	Free spectral range
G	Generation

GO	Graphene oxide
LOD	Limit of detection
NaCl	Sodium hydroxide
NaOH	Sodium hydroxide
OH	Hydroxyl
OSA	Optical spectrum analyzer
PAMAM	Polyamidoamine
PBS	Phosphate buffer solution
RMS	Root mean square
Si	Silicon
SMF	Single-mode tapered optical fiber
ssDNA	Single-stranded deoxyribose nuclease

CHAPTER 1

INTRODUCTION

1.1 Research Background

The arthropod-borne flavivirus, dengue (DENV), is one of the world's major concerns causing approximately 300 million infections per year [1]. Infection by any of its four distinct serotypes (DENV-1, DENV-2, DENV-3 and DENV-4) may lead to clinical manifestations ranging from asymptomatic infection to more severe and fatal types of dengue fever; dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS).

Conventional methods in dengue detection often rely on the presence of immunological proteins. A primary dengue infection usually triggers a slow and low titre production of IgM and IgA antibodies on the 5th day of infection, followed by a surge production of IgG a week later. On the contrary, secondary infection would be countered with a more rapid immune response as antibody titres would shoot up three days after the onset of a common fever [2]. However, the crucial set back of detecting immunological proteins is its absence during the acute phase of infection. Thus, methods as such can only detect primary infection patients with DENV from the 5^{th} day onwards after the onset of symptoms.

For early detection of the disease, diagnostics are now employing sensing systems which target antigenic determinants. It is known that DENV produces 10 different types of proteins with its 11 000 nucleotide-based genome. Three of the proteins are structural proteins for the capsid (C), membrane (prM) and envelope (E) glycoprotein, leaving the remaining 7 as non-structural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5) [2]. Given by its name, structural proteins would give rise to the formation of the virion itself. 180 identical copies of the envelope glycoproteins, for example, form the outer membrane of the virion that will facilitate the attachment of the virus to the host cell. Similar to the aforementioned invention, detection kits targeting NS1 proteins have been reported and are available in the market [3]. However, they are purely qualitative restricting its use solely for initial detection, thus, clinical monitoring and progression analysis of the infection are not possible.

Better clinical monitoring would require quantitative assessment where clinical laboratories opt for the enzyme-linked immunosorbent assay (ELISA) technique, or specifically MAC-ELISA (IgG/IgM antibody capture ELISA). The method fundamentally operates on the changes of absorbance based on the ligand-targeted antibody interaction bound on the sensing solid phase. Commercial ELISA kits today offer a detectable range of 1 – 75 ng/ml with a reported detection limit of 1 ng/ml [4]. In spite of the method's enticing capability, such an option requires a complex laboratory infrastructure, technical expertise, time consuming and financial capacity which may be limited in many countries where DENV is endemic. Real-time

polymerase chain reaction (PCR) is also another alternative for quantitative measurement of DENV as it targets the viral genome in the patient's serum [2]. However, due to the method's complexity and high cost, they have yet to be commercialized.

1.2 Problem statement and motivation

Dengue is not a foreign crisis for those who are living in the tropical region. In Malaysia, the infestation of the viral infection continues to worsen ever since its onset back in 1901. All four serotypes have been found to be co-circulating in this country with DENV II being the dominant strain [5]. As we have yet to find a specific vaccine for the virus, controlling the DENV epidemic depends solely on appropriate clinical management that should commence during the acute phase of the viral infection, which is the first three days of infection. Thus, survival of dengue patients depend highly on early, rapid and accurate diagnosis within that narrow time window. Conventional dengue diagnostics include qualitative strip kits and complex techniques like PCR and ELISA which have been found to be unreliable, time-consuming and expensive. These limitations create unnecessary delay which sadly is responsible for 70% of deaths caused by the virus and that is a serious problem [6]. It is inevitable to deny that there is still a significant need for an improved diagnostic method. The complications to the development of a robust dengue diagnostic system left medical institutes no other choice but to monitor the progression of the infection through a general blood analysis which includes platelet, white blood cell, and haematocrit counts. Although the analysis is undoubtedly helpful as supportive data, in actual, it not specific for DENV and does not represent the effect of all DENV serotype infections. Therefore, there is a need for an approach that is able to achieve greater specificity and sensitivity within a shorter amount of time and a more portable setup when compared to conventional methods namely detection strips and ELISA.

1.3 Research objectives

The research work is focused on the development of an optical sensor for sensing DENV II E protein using a functionalized single-mode tapered fiber. The objectives of the study are:

i. To design and fabricate a single-mode tapered fiber with optimized parameters for sensing bulk solutions.
ii. To design and develop a single-mode tapered fiber sensor for the detection of DENV II E proteins.
iii. To design and develop DENV II E protein sensor integrating sensing layers of graphene oxide (GO) and polyamidoamine (PAMAM) dendrimer.
iv. To analyse and compare the performance of both developed sensors

1.4 Research scope

The deployment of tapered optical fiber in sensing systems is particularly enticing as it brings forth an alternative with established compact characteristics and microstructure. Not only that, the exposed nature of tapered optical fiber creates vast opportunities of customisation and integration with other materials to fit the demands of the sensor field, today. The research work looks into the quantitative sensing of DENV II E proteins using a functionalized single-mode tapered optical fiber. DENV II strain was chosen as it has been reported to be the dominant strain in Malaysia. The selectivity of the sensor is determined by surface functionalization of bio-recognition molecules on to the tapered region, whereby in this case, Anti-DENV II E protein specific antibodies are used. For further performance enhancement of the sensing system, GO and PAMAM dendrimer are integrated individually to promote higher surface to volume ratio, homogenous adhesion and better molecular orientation. GO was chosen due to its strong core structure and the abundance of oxygenated groups on the carbon lattice network. On the other hand, the branched-like structure of PAMAM molecules terminated with amino-functional groups is predicted to provide better interaction between the immobilized protein; Anti-DENV II E protein; and the fiber surface. Both materials have great potential in facilitating a more congruent and homogeneous attachment of antibodies onto the tapered fiber. Here, the effects of GO and PAMAM towards the performance of the sensor is observed and compared by testing with different concentrations of monoclonal DENV II E protein solutions. The assessment includes measuring the sensitivity, limit of detection, dissociation constant of the sensor towards the targeted determinant, DENV II E protein, and detection time. These parameters are chosen as they are essential traits in an improved dengue diagnostic system to curb the unreliable and time-consuming methods we have today. It is to be acknowledged that assessing the shelf-life of the sensor and testing the sensor with real serum samples would strengthen the work. Unfortunately, the requirement of certain medical facilities and certification are not available for the time being. The research scope of the work is summarized in Figure 1.1.

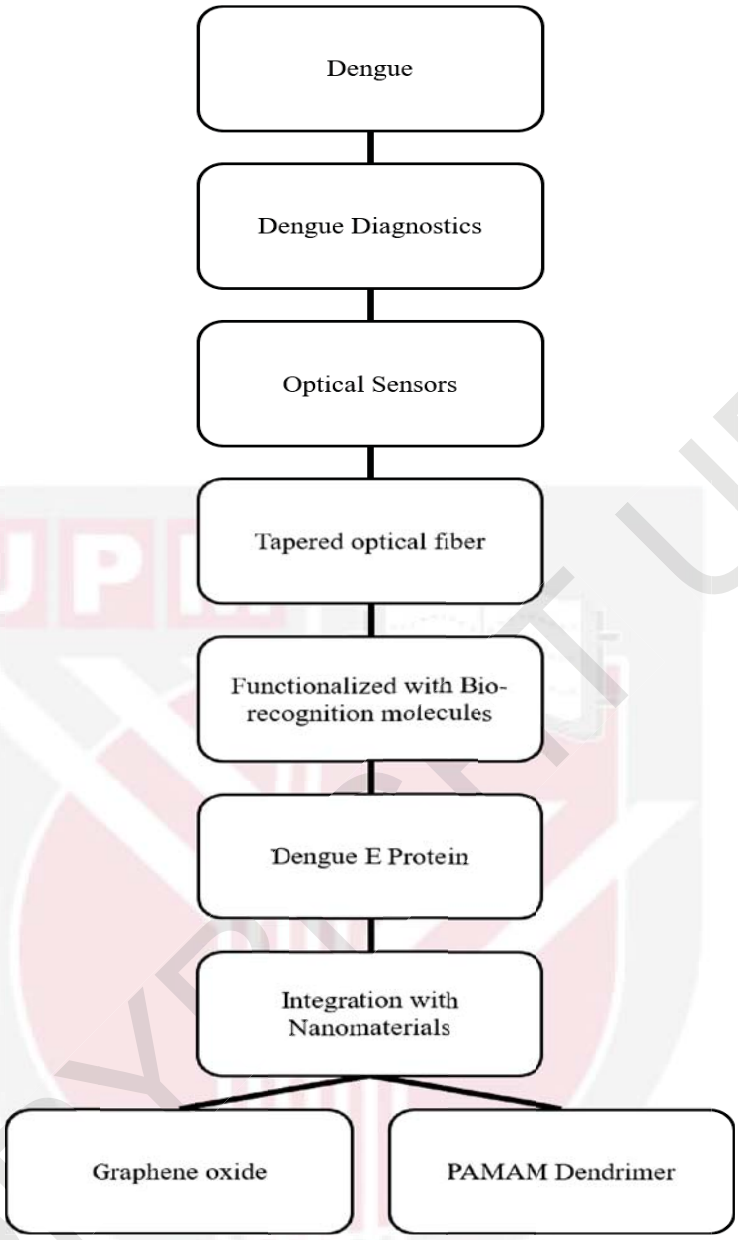

Figure 1.1 : Research scope

1.5 Organization of thesis

The content of the thesis is divided into seven chapters and are outlined as follows:

Chapter 1 delivers a brief overview about the research work. It touches on the current situation of DENV infection, challenges in the dengue diagnostics field, and motivations in conducting the work.

Chapter 2 describes the conventional methods and current trends in dengue diagnostics. Following that is an extensive review on the sensing mechanism of tapered optical fiber based sensors as well as previous studies that are relevant. The emerging technology of nanomaterial integration within optical sensing systems and its applications are also presented in this chapter.

Chapter 3 elaborates on the fabrication of the tapered optical fibers and the characterization of its geometrical dimension to obtain optimum sensitivity. Here, the effects of waist diameter and waist length towards the performance of the tapered optical fiber sensor are experimentally investigated.

Chapter 4 discusses on the functionalization of bio-recognition molecules onto the surface of the tapered optical fiber in order to enhance the selectivity of the sensor. Acknowledging that fact that promoting molecular assembly on the tapered optical fiber is a delicate process, preliminary investigation and optimization of the surface modification method are conducted with Silane-PEG-Biotin and Avidin first before the immobilization of recombinant DENV antibodies.

Chapter 5 describes the subsequent step to what has been discussed in chapter 4, where recombinant DENV II E protein specific antibodies are immobilized onto the tapered optical fiber. It also highlights the performance of the functionalized tapered optical fiber in sensing DENV II E proteins at different concentrations. The performance of the sensor is analyzed by measuring the sensitivity and limit of detection.

Chapter 6 elaborates on the performance of the sensor when integrated with GO and PAMAM dendrimer, individually. It begins with optimizing the deposition method of both nanomaterials by monitoring wavelength shift throughout time. Performance analysis is also conducted and presented in this chapter.

Chapter 7 concludes the study by summarizing key points of the research and introduces recommendations for future work.

REFERENCES

[1] N. E. A. Murray, M. B. Quam, and A. Wilder-Smith, "Epidemiology of dengue: past, present and future prospects," *Clin. Epidemiol.*, vol. 5, pp. 299–309, Aug. 2013.

[2] M. G. Guzmán and G. Kourí, "Dengue diagnosis, advances and challenges," *Int. J. Infect. Dis.*, vol. 8, no. 2, pp. 69–80, Mar. 2004.

[3] S. Chaterji, J. C. Allen, A. Chow, Y.-S. Leo, and E.-E. Ooi, "Evaluation of the NS1 Rapid Test and the WHO Dengue Classification Schemes for Use as Bedside Diagnosis of Acute Dengue Fever in Adults," *Am. J. Trop. Med. Hyg.*, vol. 84, no. 2, pp. 224–228, Feb. 2011.

[4] S. Alcon, A. Talarmin, M. Debruyne, A. Falconar, V. Deubel, and M. Flamand, "Enzyme-Linked Immunosorbent Assay Specific to Dengue Virus Type 1 Nonstructural Protein NS1 Reveals Circulation of the Antigen in the Blood during the Acute Phase of Disease in Patients Experiencing Primary or Secondary Infections," *J. Clin. Microbiol.*, vol. 40, no. 2, pp. 376–381, Feb. 2002.

[5] L.-C. Ng, Y. Chem, C. Koo, R. N. B. Mudin, F. M. Amin, K.-S. Lee, and C. C. Kheong, "2013 Dengue Outbreaks in Singapore and Malaysia Caused by Different Viral Strains," *Am. J. Trop. Med. Hyg.*, vol. 92, no. 6, pp. 1150–1155, Jun. 2015.

[6] Y. L. Woon, C. P. Hor, N. Hussin, A. Zakaria, P. P. Goh, and W. K. Cheah, "A Two-Year Review on Epidemiology and Clinical Characteristics of Dengue Deaths in Malaysia, 2013-2014," *PLoS Negl. Trop. Dis.*, vol. 10, no. 5, p. e0004575, May 2016.

[7] M. S. Diamond, T. C. Pierson, S. Shresta, L. R. Macareo, M. C. Cassetti, V. C. N. Van, P. Y. Shi, B. Wills, C. P. Simmons, and A. M. de Silva, "Molecular Insight into Dengue Virus Pathogenesis and Its Implications for Disease Control," *Cell*, vol. 162, no. 3, pp. 488–492, Jul. 2015.

[8] C. T. Jones, L. Ma, J. W. Burgner, T. D. Groesch, C. B. Post, and R. J. Kuhn, "Flavivirus capsid is a dimeric alpha-helical protein.," *J. Virol.*, vol. 77, no. 12, pp. 7143–9, Jun. 2003.

[9] I. A. Rodenhuis-Zybert, J. Wilschut, and J. M. Smit, "Dengue virus life cycle: viral and host factors modulating infectivity," *Cell. Mol. Life Sci.*, vol. 67, no. 16, pp. 2773–2786, 2010.

[10] S.-S. Wong, G. Haqshenas, E. J. Gowans, and J. Mackenzie, "The dengue virus M protein localises to the endoplasmic reticulum and forms oligomers," *FEBS Lett.*, vol. 586, no. 7, pp. 1032–1037, Apr. 2012.

[11] D. E. Klein, J. L. Choi, and S. C. Harrison, “Structure of a dengue virus envelope protein late-stage fusion intermediate.,” *J. Virol.*, vol. 87, no. 4, pp. 2287–93, Feb. 2013.

[12] T. Walker, P. H. Johnson, L. A. Moreira, I. Iturbe-Ormaetxe, F. D. Frentiu, C. J. McMeniman, Y. S. Leong, Y. Dong, J. Axford, P. Kriesner, A. L. Lloyd, S. A. Ritchie, S. L. O/’Neill, and A. A. Hoffmann, “The wMel Wolbachia strain blocks dengue and invades caged Aedes aegypti populations,” *Nature*, vol. 476, no. 7361, pp. 450–453, Aug. 2011.

[13] A. A. Hoffmann, B. L. Montgomery, J. Popovici, I. Iturbe-Ormaetxe, P. H. Johnson, F. Muzzi, M. Greenfield, M. Durkan, Y. S. Leong, Y. Dong, H. Cook, J. Axford, A. G. Callahan, N. Kenny, C. Omodei, E. A. McGraw, P. A. Ryan, S. A. Ritchie, M. Turelli, and S. L. O/’Neill, “Successful establishment of Wolbachia in Aedes populations to suppress dengue transmission,” *Nature*, vol. 476, no. 7361, pp. 454–457, Aug. 2011.

[14] A. B. Hall, S. Basu, X. Jiang, Y. Qi, V. A. Timoshevskiy, J. K. Biedler, M. V Sharakhova, R. Elahi, M. A. E. Anderson, X.-G. Chen, I. V Sharakhov, Z. N. Adelman, and Z. Tu, “A male-determining factor in the mosquito Aedes aegypti,” *Science (80-.).*, vol. 348, no. 6240, p. 1268 LP-1270, Jun. 2015.

[15] S.-J. L. Wu, G. Grouard-Vogel, W. Sun, J. R. Mascola, E. Brachtel, R. Putvatana, M. K. Louder, L. Filgueira, M. A. Marovich, H. K. Wong, A. Blauvelt, G. S. Murphy, M. L. Robb, B. L. Innes, D. L. Birx, C. G. Hayes, and S. S. Frankel, “Human skin Langerhans cells are targets of dengue virus infection,” *Nat Med*, vol. 6, no. 7, pp. 816–820, Jul. 2000.

[16] K. Jessie, M. Y. Fong, S. Devi, S. K. Lam, and K. T. Wong, “Localization of Dengue Virus in Naturally Infected Human Tissues, by Immunohistochemistry and In Situ Hybridization,” *J. Infect. Dis.*, vol. 189, no. 8, pp. 1411–1418, Apr. 2004.

[17] Y. Modis, S. Ogata, D. Clements, and S. C. Harrison, “Structure of the dengue virus envelope protein after membrane fusion,” *Nature*, vol. 427, no. 6972, pp. 313–319, Jan. 2004.

[18] G. Screaton, J. Mongkolsapaya, S. Yacoub, and C. Roberts, “New insights into the immunopathology and control of dengue virus infection,” *Nat Rev Immunol*, vol. 15, no. 12, pp. 745–759, Dec. 2015.

[19] B. E. E. Martina, P. Koraka, and A. D. M. E. Osterhaus, “Dengue Virus Pathogenesis: an Integrated View,” *Clin. Microbiol. Rev.* , vol. 22, no. 4, pp. 564–581, Oct. 2009.

[20] A. Srikiatkhachorn, “Plasma leakage in dengue haemorrhagic fever,” *Thromb. Haemost.*, vol. 102, no. 6, pp. 1042–1049, 2009.

[21] S. Kalayanarooj, "Clinical Manifestations and Management of Dengue/DHF/DSS," *Trop. Med. Health*, vol. 39, no. 4 Suppl, pp. 83–87, Dec. 2011.

[22] M. P. G. Mourão, M. V. G. Lacerda, V. O. Macedo, M. P. G. Mourão, M. V. G. Lacerda, V. O. Macedo, and J. B. Santos, "Thrombocytopenia in patients with dengue virus infection in the Brazilian Amazon," *Platelets*, vol. 18, no. 8, pp. 605–612, Jan. 2007.

[23] S. Yacoub, H. Wertheim, C. P. Simmons, G. Screaton, and B. Wills, "Cardiovascular manifestations of the emerging dengue pandemic," *Nat Rev Cardiol*, vol. 11, no. 6, pp. 335–345, Jun. 2014.

[24] J. D. Stanaway, D. S. Shepard, E. A. Undurraga, Y. A. Halasa, L. E. Coffeng, O. J. Brady, S. I. Hay, N. Bedi, I. M. Bensenor, C. A. Castañeda-Orjuela, T.-W. Chuang, K. B. Gibney, Z. A. Memish, A. Rafay, K. N. Ukwaja, N. Yonemoto, and C. J. L. Murray, "The global burden of dengue: an analysis from the Global Burden of Disease Study 2013," *Lancet Infect. Dis.*, vol. 16, no. 6, pp. 712–723, Mar. 2017.

[25] D. W. Vaughn, A. Nisalak, S. Kalayanarooj, T. Solomon, N. M. Dung, A. Cuzzubbo, and P. L. Devine, "Evaluation of a Rapid Immunochromatographic Test for Diagnosis of Dengue Virus Infection," *J. Clin. Microbiol.*, vol. 36, no. 1, pp. 234–238, Jan. 1998.

[26] A. J. Cuzzubbo, T. P. Endy, A. Nisalak, S. Kalayanarooj, D. W. Vaughn, S. A. Ogata, D. E. Clements, and P. L. Devine, "Use of Recombinant Envelope Proteins for Serological Diagnosis of Dengue Virus Infection in an Immunochromatographic Assay," *Clin. Diagn. Lab. Immunol.*, vol. 8, no. 6, pp. 1150–1155, Nov. 2001.

[27] F. M. Kassim, M. N. Izati, T. TgRogayah, Y. M. Apandi, and Z. Saat, "Use of dengue NS1 antigen for early diagnosis of dengue virus infection," *Southeast Asian J. Trop. Med. Public Health*, vol. 42, no. 3, pp. 562–569, 2011.

[28] T. M. Conceição, A. T. Da Poian, and M. H. F. Sorgine, "A real-time PCR procedure for detection of dengue virus serotypes 1, 2, and 3, and their quantitation in clinical and laboratory samples.," *J. Virol. Methods*, vol. 163, no. 1, pp. 1–9, Jan. 2010.

[29] R. J. Welch, G.-J. J. Chang, and C. M. Litwin, "Comparison of a commercial dengue IgM capture ELISA with dengue antigen focus reduction microneutralization test and the Centers for Disease Control dengue IgM capture-ELISA.," *J. Virol. Methods*, vol. 195, pp. 247–9, Jan. 2014.

[30] R. W. Peeling, H. Artsob, J. L. Pelegrino, P. Buchy, M. J. Cardosa, S. Devi, D. a. Enria, J. Farrar, D. J. Gubler, M. G. Guzman, S. B. Halstead, E. Hunsperger, S. Kliks, H. S. Margolis, C. M. Nathanson, V. C. Nguyen, N. Rizzo, S. Vázquez, and S. Yoksan, "Evaluation of diagnostic tests: dengue," *Nat. Rev. Microbiol.*, vol. 8, no. 12, pp. S30–S37, Dec. 2010.

[31] I. T. Cavalcanti, B. V. M. Silva, N. G. Peres, P. Moura, M. D. P. T. Sotomayor, M. I. F. Guedes, and R. F. Dutra, "A disposable chitosan-modified carbon fiber electrode for dengue virus envelope protein detection," *Talanta*, vol. 91, pp. 41–46, Mar. 2012.

[32] I. T. Cavalcanti, M. I. F. Guedes, M. D. P. T. Sotomayor, H. Yamanaka, and R. F. Dutra, "A label-free immunosensor based on recordable compact disk chip for early diagnostic of the dengue virus infection," *Biochem. Eng. J.*, vol. 67, pp. 225–230, 2012.

[33] A. R. Camara, P. M. P. Gouvêa, A. C. M. S. Dias, A. M. B. Braga, R. F. Dutra, R. E. de Araujo, and I. C. S. Carvalho, "Dengue immunoassay with an LSPR fiber optic sensor," *Opt. Express*, vol. 21, no. 22, pp. 27023–27031, 2013.

[34] B. S. Kawasaki, K. O. Hill, and R. G. Lamont, "Biconical-taper single-mode fiber coupler," *Opt. Lett.*, vol. 6, no. 7, pp. 327–328, 1981.

[35] A. Kumar, T. V. B. Subrahmanyam, A. D. Sharma, K. Thyagarajan, B. P. Pal, and I. C. Goyal, "Novel refractometer using a tapered optical fibre," *Electronics Letters*, vol. 20, no. 13. pp. 534–535, 1984.

[36] S. Sidhik, J. V Ittiarah, and T. K. Gangopadhyay, "Design and Analysis of Chemically Etched and Biconically Tapered Fiber for Chemical Sensing Application," in *IEM Optronix*, 2015, pp. 173–179.

[37] S. Mononobe, R. U. Maheswari, and M. Ohtsu, "Fabrication of a pencil-shaped fiber probe with a nanometric protrusion from a metal film for near-field optical microscopy," *Opt. Express*, vol. 1, no. 8, pp. 229–233, 1997.

[38] T. K. Gangopadhyay, A. Halder, S. Das, M. C. Paul, M. Pal, M. Salza, and G. Gagliardi, "Fabrication of tapered single mode fiber by chemical etching and used as a chemical sensor based on evanescent field absorption," 2010, vol. 8173, pp. 817310–817321.

[39] J. D. Love, W. M. H. Gonthier, W. J. Stewart, R. J. Black, and S. L. F., "Tapered single-mode fibres and devices. I. Adiabaticity criteria," *IEE Proc. J - Optoelectron.*, vol. 138, no. 343–354, 1991.

[40] M. Ahmad and L. L. Hench, "Effect of taper geometries and launch angle on evanescent wave penetration depth in optical fibers.," *Biosens. Bioelectron.*, vol. 20, no. 7, pp. 1312–9, Jan. 2005.

[41] J. Miller, A. Castaneda, H. K. Lee, M. Sanchez, A. Ortiz, E. Almaz, T. Z. Almaz, S. Murinda, W.-J. Lin, and E. Salik, "Biconically Tapered Fiber Optic Probes for Rapid Label-Free Immunoassays," *Biosensors*, vol. 5, no. 2. pp. 158–171, 2015.

[42] Y. Huang, Z. Tian, L.-P. Sun, D. Sun, J. Li, Y. Ran, and B.-O. Guan, "High-sensitivity DNA biosensor based on optical fiber taper interferometer coated with conjugated polymer tentacle," *Opt. Express*, vol. 23, no. 21, pp. 26962–26968, 2015.

[43] D. Sun, T. Guo, Y. Ran, Y. Huang, and B.-O. Guan, "In-situ DNA hybridization detection with a reflective microfiber grating biosensor," *Biosens. Bioelectron.*, vol. 61, pp. 541–546, Nov. 2014.

[44] C. Beres, F. V. B. de Nazaré, N. C. C. de Souza, M. A. L. Miguel, and M. M. Werneck, "Tapered plastic optical fiber-based biosensor – Tests and application," *Biosens. Bioelectron.*, vol. 30, no. 1, pp. 328–332, Dec. 2011.

[45] T. K. Yadav, R. Narayanaswamy, M. H. Abu Bakar, Y. M. Kamil, and M. A. Mahdi, "Single mode tapered fiber-optic interferometer based refractive index sensor and its application to protein sensing.," *Opt. Express*, vol. 22, no. 19, pp. 22802–7, Sep. 2014.

[46] A. P. de Silva, H. Q. N. Gunaratne, T. Gunnlaugsson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher, and T. E. Rice, "Signaling Recognition Events with Fluorescent Sensors and Switches," *Chem. Rev.*, vol. 97, no. 5, pp. 1515–1566, Aug. 1997.

[47] R. Elghanian, J. J. Storhoff, R. C. Mucic, R. L. Letsinger, and C. A. Mirkin, "Selective Colorimetric Detection of Polynucleotides Based on the Distance-Dependent Optical Properties of Gold Nanoparticles," *Science (80-.).*, vol. 277, no. 5329, p. 1078 LP-1081, Aug. 1997.

[48] N. Nath and A. Chilkoti, "A Colorimetric Gold Nanoparticle Sensor To Interrogate Biomolecular Interactions in Real Time on a Surface," *Anal. Chem.*, vol. 74, no. 3, pp. 504–509, Feb. 2002.

[49] M. Nasrollahzadeh, F. Babaei, P. Fakhri, and B. Jaleh, "Synthesis, characterization, structural, optical properties and catalytic activity of reduced graphene oxide/copper nanocomposites," *RSC Adv.*, vol. 5, no. 14, pp. 10782–10789, 2015.

[50] L. Staudenmaier, "Verfahren zur Darstellung der Graphitsäure," *Berichte der Dtsch. Chem. Gesellschaft*, vol. 31, no. 2, pp. 1481–1487, May 1898.

[51] U. Hofmann and E. König, "Untersuchungen über Graphitoxyd," *Zeitschrift für Anorg. und Allg. Chemie*, vol. 234, no. 4, pp. 311–336, Dec. 1937.

[52] B. C. Brodie, “On the Atomic Weight of Graphite,” *Philos. Trans. R. Soc. London* , vol. 149, pp. 249–259, Jan. 1859.

[53] W. S. Hummers and R. E. Offeman, “Preparation of Graphitic Oxide,” *J. Am. Chem. Soc.*, vol. 80, no. 6, p. 1339, Mar. 1958.

[54] Chengzhou Zhu and Shaojun Dong, “Recent progress in graphene-based nanomaterials as advanced electrocatalysts towards oxygen reduction reaction,” *Nanoscale*, vol. 5, pp. 1753–1767, 2013.

[55] A. Ganguly, S. Sharma, P. Papakonstantinou, and J. Hamilton, “Probing the Thermal Deoxygenation of Graphene Oxide Using High-Resolution In Situ X-ray-Based Spectroscopies,” *J. Phys. Chem. C*, vol. 115, no. 34, pp. 17009–17019, Sep. 2011.

[56] J. I. Paredes, S. Villar-Rodil, P. Solís-Fernández, A. Martínez-Alonso, and J. M. D. Tascón, “Atomic Force and Scanning Tunneling Microscopy Imaging of Graphene Nanosheets Derived from Graphite Oxide,” *Langmuir*, vol. 25, no. 10, pp. 5957–5968, May 2009.

[57] R. P. Gandhiraman, D. Nordlund, C. Javier, J. E. Koehne, B. Chen, and M. Meyyappan, “X-ray Absorption Study of Graphene Oxide and Transition Metal Oxide Nanocomposites,” *J. Phys. Chem. C*, vol. 118, no. 32, pp. 18706–18712, Aug. 2014.

[58] Y. Si and E. T. Samulski, “Synthesis of Water Soluble Graphene,” *Nano Lett.*, vol. 8, no. 6, pp. 1679–1682, Jun. 2008.

[59] D. R. Dreyer, S. Park, C. W. Bielawski, and R. S. Ruoff, “The chemistry of graphene oxide,” *Chem. Soc. Rev.*, vol. 39, no. 1, pp. 228–240, 2010.

[60] O. C. Compton and S. T. Nguyen, “Graphene Oxide, Highly Reduced Graphene Oxide, and Graphene: Versatile Building Blocks for Carbon-Based Materials,” *Small*, vol. 6, no. 6, pp. 711–723, Mar. 2010.

[61] J. S. Park, H.-K. Na, D.-H. Min, and D.-E. Kim, “Desorption of single-stranded nucleic acids from graphene oxide by disruption of hydrogen bonding,” *Analyst*, vol. 138, no. 6, pp. 1745–1749, 2013.

[62] M. A. A. Rosli, P. T. Arasu, H. N. Lim, and A. S. M. Noor, “Dynamic response of tapered optical fiber coated with graphene oxide for detecting aqueous ethanol,” in *IEEE 6th International Conference on Photonics*, 2016.

[63] S. H. Girei, A. A. Shabaneh, H. M. Lim, N. H. Huang, M. A. Mahdi, and M. H. Yaacob, “Absorbance response of graphene oxide coated on tapered multimode optical fiber towards liquid ethanol,” *J. Eur. Opt. Soc. - Rapid Publ. Vol 10*, 2015.

[64] A. A. Shabaneh, S. H. Girei, P. T. Arasu, W. B. W. A. Rahman, A. A. A. Bakar, A. Z. Sadek, H. N. Lim, N. M. Huang, and M. H. Yaacob, "Reflectance response of tapered optical fiber coated with graphene oxide nanostructured thin film for aqueous ethanol sensing," *Opt. Commun.*, vol. 331, pp. 320–324, 2014.

[65] H. Arima and K. Motoyama, "Recent Findings Concerning PAMAM Dendrimer Conjugates with Cyclodextrins as Carriers of DNA and RNA," *Sensors (Basel).*, vol. 9, no. 8, pp. 6346–6361, Aug. 2009.

[66] J. Satija, B. Karunakaran, and S. Mukherji, "A dendrimer matrix for performance enhancement of evanescent wave absorption-based fiber-optic biosensors," *RSC Adv.*, vol. 4, no. 31, pp. 15841–15848, 2014.

[67] E. Sorsak, J. V. Valh, S. K. Urek, and A. Lobnik, "Application of PAMAM dendrimers in optical sensing," *Analyst*, vol. 140, no. 4, pp. 976–989, 2015.

[68] J. Li, H. Li, Y. Zhao, H. Hu, and Q. Wang, "Hollow fiber taper with a silver micro-sphere used as refractive index sensor," *Opt. Commun.*, vol. 318, no. 11, pp. 7–10, May 2014.

[69] L. I. Espada, M. Shadaram, J. Robillard, and K. H. Pannell, "Ferrocenylenesilylene Polymers as Coatings for Tapered Optical-Fiber Gas Sensors," *J. Inorg. Organomet. Polym.*, vol. 10, no. 4, pp. 169–176, 2000.

[70] J. D. Black, R.J.; Lacroix, S.; Gonthier, F.; Love, "Tapered single-mode fibres and devices. Part 2: Experimental and theoretical quantification," in *IEE Proceedings J (Optoelectronics)*, 1991, pp. 355–364.

[71] M. Z. Muhammad, a. a. Jasim, H. Ahmad, H. Arof, and S. W. Harun, "Non-adiabatic silica microfiber for strain and temperature sensors," *Sensors Actuators A Phys.*, vol. 192, pp. 130–132, Apr. 2013.

[72] B. Musa, Y. Mustapha Kamil, M. H. Abu Bakar, A. S. Mohd Noor, A. Ismail, and M. A. Mahdi, "Investigating the effect of taper length on sensitivity of the tapered-fiber based temperature sensor," *J. Teknol.*, vol. 78, no. 3, pp. 135–140, 2016.

[73] W. B. Ji, Y. C. Tan, B. Lin, S. C. Tjin, and K. K. Chow, "Nonadiabatically Tapered Microfiber Sensor With Ultrashort Waist," *IEEE Photonics Technology Letters*, vol. 26, no. 22. pp. 2303–2306, 2014.

[74] W. Bin, H. Huan, S. Chuan, K. Kee, W. Bin Ji, H. H. Liu, S. C. Tjin, K. K. Chow, and A. Lim, "Ultra-high sensitivity refractive index sensor based on optical microfiber," *Photonics Technol. Lett.*, vol. 24, no. 20, 2012.

[75] A. E. Fenster, D. N. Harpp, and J. A. Schwarcz, "A useful model for the 'lock and key' analogy," *J. Chem. Educ.*, vol. 61, no. 11, p. 967, Nov. 1984.

[76] Y. Mustapha Kamil, M. H. Abu Bakar, M. A. Mustapa, M. H. Yaacob, A. Syahir, and M. A. Mahdi, "Sensitive and Specific Protein Sensing Using Single-Mode Tapered Fiber Immobilized With Biorecognition Molecules," *IEEE Photonics J.*, vol. 7, no. 6, pp. 1–9, Dec. 2015.

[77] L. Chaiet and F. J. Wolf, "The properties of streptavidin, a biotin-binding protein produced by Streptomycetes," *Arch. Biochem. Biophys.*, vol. 106, pp. 1–5, 1964.

[78] Y. Mu, H. Zhang, X. Zhao, D. Song, Z. Wang, J. Sun, M. Li, and Q. Jin, "An Optical Biosensor for Monitoring Antigen Recognition Based on Surface Plasmon Resonance Using Avidin-Biotin System," *Sensors*, vol. 1, no. 3, pp. 91–101, Aug. 2001.

[79] A. Heidari, Y.-J. Yoon, W.-T. Park, P.-C. Su, J. Miao, J. T. M. Lin, and M. K. Park, "Biotin-Streptavidin Binding Interactions of Dielectric Filled Silicon Bulk Acoustic Resonators for Smart Label-Free Biochemical Sensor Applications," *Sensors (Basel).*, vol. 14, no. 3, pp. 4585–4598, Mar. 2014.

[80] V. Popescu and E. I. Muresan, "Performances of Chitosan Grafted onto Surface of Polyacrylonitrile Functionalized through Amination Reactions," *Ind. Eng. Chem. Res.*, vol. 52, no. 37, pp. 13252–13263, Sep. 2013.

[81] S. L. Warring, D. A. Beattie, and A. J. McQuillan, "Surficial Siloxane-to-Silanol Interconversion during Room-Temperature Hydration/Dehydration of Amorphous Silica Films Observed by ATR-IR and TIR-Raman Spectroscopy," *Langmuir*, vol. 32, no. 6, pp. 1568–1576, Feb. 2016.

[82] P. F. McMillan and R. L. Remmele, "Hydroxyl sites in SiO ₂ glass; a note on infrared and Raman spectra," *Am. Mineral.*, vol. 71, no. 5–6, p. 772 LP-778, Jun. 1986.

[83] Y. Liu, Y. Li, X.-M. Li, and T. He, "Kinetics of (3-Aminopropyl)triethoxylsilane (APTES) Silanization of Superparamagnetic Iron Oxide Nanoparticles," *Langmuir*, vol. 29, no. 49, pp. 15275–15282, Dec. 2013.

[84] R. G. Acres, A. V Ellis, J. Alvino, C. E. Lenahan, D. A. Khodakov, G. F. Metha, and G. G. Andersson, "Molecular Structure of 3-Aminopropyltriethoxysilane Layers Formed on Silanol-Terminated Silicon Surfaces," *J. Phys. Chem. C*, vol. 116, no. 10, pp. 6289–6297, Mar. 2012.

[85] M. A. G. and G. F. G. and I. N. A. and M. Y. A. and T. V Antropova, "Structure and spectral properties of the silver-containing high-silica glasses," *J. Phys. Conf. Ser.*, vol. 741, no. 1, p. 12144, 2016.

[86] M. Gynba, M. Keranen, M. Kozaneckhi, and B. B. Kosmowski, "Raman investigation of hybrid polymer thin films," *Mater. Sci.*, vol. 23, no. 1, pp. 30–39, 2005.

[87] N. A. Lapin and Y. J. Chabal, “Infrared Characterization of Biotinylated Silicon Oxide Surfaces, Surface Stability and Specific Attachment of Streptavidin,” *J. Phys. Chem. B*, vol. 113, no. 25, pp. 8776–8783, Jun. 2009.

[88] Y. Sun, M. Yanagisawa, M. Kunimoto, M. Nakamura, and T. Homma, “Estimated phase transition and melting temperature of APTES self-assembled monolayer using surface-enhanced anti-stokes and stokes Raman scattering,” *Appl. Surf. Sci.*, vol. 363, pp. 572–577, 2016.

[89] D. Aureau, Y. Varin, K. Roodenko, O. Seitz, O. Pluchery, and Y. J. Chabal, “Controlled Deposition of Gold Nanoparticles on Well-Defined Organic Monolayer Grafted on Silicon Surfaces,” *J. Phys. Chem. C*, vol. 114, no. 33, pp. 14180–14186, Aug. 2010.

[90] Z.-H. Wang and G. Jin, “Silicon surface modification with a mixed silanes layer to immobilize proteins for biosensor with imaging ellipsometry,” *Colloids Surfaces B Biointerfaces*, vol. 34, no. 3, pp. 173–177, 2004.

[91] N. S. K. Gunda, M. Singh, L. Norman, K. Kaur, and S. K. Mitra, “Optimization and characterization of biomolecule immobilization on silicon substrates using (3-aminopropyl)triethoxysilane (APTES) and glutaraldehyde linker,” *Appl. Surf. Sci.*, vol. 305, pp. 522–530, 2014.

[92] O. Barbosa, C. Ortiz, A. Berenguer-Murcia, R. Torres, R. C. Rodrigues, and R. Fernandez-Lafuente, “Glutaraldehyde in bio-catalysts design: a useful crosslinker and a versatile tool in enzyme immobilization,” *RSC Adv.*, vol. 4, no. 4, pp. 1583–1600, 2014.

[93] M. P. Byrne and W. E. Stites, “Chemically crosslinked protein dimers: stability and denaturation effects.,” *Protein Sci.*, vol. 4, no. 12, pp. 2545–2558, Dec. 1995.

[94] N. Koshida, *Device Applications of Silicon Nanocrystals and Nanostructures*. 2009.

[95] S. Mishra, D. Chaturvedi, P. Tandon, V. P. Gupta, A. P. Ayala, S. B. Honorato, and H. W. Siesler, “Molecular Structure and Vibrational Spectroscopic Investigation of Secnidazole Using Density Functional Theory,” *J. Phys. Chem. A*, vol. 113, no. 1, pp. 273–281, Jan. 2009.

[96] M. J. Murray, F. F. Cleveland, and R. H. Saunders, “Raman Spectra of Some Aromatic Carbonyl and Nitro Compounds,” *J. Am. Chem. Soc.*, vol. 64, no. 5, pp. 1181–1184, May 1942.

[97] P. Lagant, G. Vergotten, G. Fleury, and M.-H. Loucheux-Lefbvre, “Raman spectroscopy and normal vibrations of peptides,” *Eur. J. Biochem.*, vol. 139, no. 1, pp. 137–148, Feb. 1984.

[98] L. D. S. Yadav, *Organic Spectroscopy*. 2013.

[99] S. Nakashima, T. Ogura, and T. Kitagawa, “Infrared and Raman spectroscopic investigation of the reaction mechanism of cytochrome c oxidase,” *Biochim. Biophys. Acta - Bioenerg.*, vol. 1847, no. 1, pp. 86–97, 2015.

[100] E. Podstawka, E. Sikorska, L. M. Proniewicz, and B. Lammek, “Raman and surface-enhanced Raman spectroscopy investigation of vasopressin analogues containing 1-aminocyclohexane-1-carboxylic acid residue,” *Biopolymers*, vol. 83, no. 2, pp. 193–203, Oct. 2006.

[101] G. Vidarsson, G. Dekkers, and T. Rispens, “IgG Subclasses and Allotypes: From Structure to Effector Functions,” *Front. Immunol.*, vol. 5, p. 520, Oct. 2014.

[102] V. Irani, A. J. Guy, D. Andrew, J. G. Beeson, P. A. Ramsland, and J. S. Richards, “Molecular properties of human IgG subclasses and their implications for designing therapeutic monoclonal antibodies against infectious diseases,” *Mol. Immunol.*, vol. 67, no. 2, pp. 171–182, 2015.

[103] E. Seymour, G. G. Daaboul, X. Zhang, S. M. Scherr, N. L. Ünlü, J. H. Connor, and M. S. Ünlü, “DNA-Directed Antibody Immobilization for Enhanced Detection of Single Viral Pathogens,” *Anal. Chem.*, vol. 87, no. 20, pp. 10505–10512, Oct. 2015.

[104] J. Ren, K. Tian, L. Jia, X. Han, and M. Zhao, “Rapid Covalent Immobilization of Proteins by Phenol-Based Photochemical Cross-Linking,” *Bioconjug. Chem.*, vol. 27, no. 10, pp. 2266–2270, Oct. 2016.

[105] Kengne-Momo R, D. P, L. F, J. Y, P. J, D.-T. M, and T. G, “Protein Interactions Investigated by the Raman Spectroscopy for Biosensor Applications,” *Int. J. Spectrosc.*, vol. 2012, p. 7, 2012.

[106] K. Jiang, A. Eitan, L. S. Schadler, P. M. Ajayan, R. W. Siegel, N. Grobert, M. Mayne, M. Reyes-Reyes, H. Terrones, and M. Terrones, “Selective Attachment of Gold Nanoparticles to Nitrogen-Doped Carbon Nanotubes,” *Nano Lett.*, vol. 3, no. 3, pp. 275–277, Mar. 2003.

[107] F. X. Heinz, C. W. Mandl, H. Holzmann, C. Kunz, B. A. Harris, F. Rey, and S. C. Harrison, “The flavivirus envelope protein E: isolation of a soluble form from tick-borne encephalitis virus and its crystallization.,” *J. Virol.*, vol. 65, no. 10, pp. 5579–5583, Oct. 1991.

[108] G. T. Hermanson, “Chapter 11 - (Strept)avidin–Biotin Systems BT - Bioconjugate Techniques (Third edition),” Boston: Academic Press, 2013, pp. 465–505.

[109] S. Demeo, “Mathematically Modeling Dilution,” *Chem. Educ.*, vol. 1, no. 2, pp. 1–5, 1996.

[110] S. I. de la Cruz-Hernández, H. Flores-Aguilar, S. González-Mateos, I. López-Martinez, C. Alpuche-Aranda, J. E. Ludert, and R. M. del Angel, "Determination of Viremia and Concentration of Circulating Nonstructural Protein 1 in Patients Infected with Dengue Virus in Mexico," *Am. J. Trop. Med. Hyg.*, vol. 88, no. 3, pp. 446–454, Mar. 2013.

[111] A. R. Camara, P. M. P. Gouvêa, A. C. M. S. Dias, A. M. B. Braga, R. F. Dutra, R. E. De Araujo, and I. C. S. Carvalho, "Dengue immunoassay with an LSPR fiber optic sensor," vol. 21, no. 22, pp. 27023–27031, 2013.

[112] N. V Zaytseva, R. A. Montagna, and A. J. Baeumner, "Microfluidic Biosensor for the Serotype-Specific Detection of Dengue Virus RNA," *Anal. Chem.*, vol. 77, no. 23, pp. 7520–7527, Dec. 2005.

[113] D. Yang, A. Singh, H. Wu, and R. Kroe-Barrett, "Comparison of biosensor platforms in the evaluation of high affinity antibody-antigen binding kinetics," *Anal. Biochem.*, vol. 508, pp. 78–96, 2016.

[114] "'Plenty of room' revisited," *Nat Nano*, vol. 4, no. 12, p. 781, Dec. 2009.

[115] C. K. Chua and M. Pumera, "The reduction of graphene oxide with hydrazine: elucidating its reductive capability based on a reaction-model approach," *Chem. Commun.*, vol. 52, no. 1, pp. 72–75, 2016.

[116] N. M. Huang, H. N. Lim, C. H. Chia, M. A. Yarmo, and M. R. Muhamad, "Simple room-temperature preparation of high-yield large-area graphene oxide," *Int. J. Nanomedicine*, vol. 6, pp. 3443–3448, Dec. 2011.

[117] M. Krueger, S. Berg, D. Stone, E. Strelcov, D. A. Dikin, J. Kim, L. J. Cote, J. Huang, and A. Kolmakov, "Drop-Casted Self-Assembling Graphene Oxide Membranes for Scanning Electron Microscopy on Wet and Dense Gaseous Samples," *ACS Nano*, vol. 5, no. 12, pp. 10047–10054, Dec. 2011.

[118] K. Kashiwagi, S. Yamashita, and S. Y. Set, "In-situ monitoring of optical deposition of carbon nanotubes onto fiber end," *Opt. Express*, vol. 17, no. 7, pp. 5711–5715, 2009.

[119] J. Wang, Z. Luo, M. Zhou, C. Ye, H. Fu, Z. Cai, H. Cheng, H. Xu, and W. Qi, "Evanescent-Light Deposition of Graphene Onto Tapered Fibers for Passive Q-Switch and Mode-Locker," *IEEE Photonics Journal*, vol. 4, no. 5. pp. 1295–1305, 2012.

[120] K. Matsuda, Y. Yamaguchi, N. Morita, T. Matsunobe, and M. Yoshikawa, "Characterization of fluorine-doped silicon dioxide films by Raman spectroscopy and Electron-spin resonance," *Thin Solid Films*, vol. 515, no. 17, pp. 6682–6685, 2007.

[121] G.-L. Lan, P. K. Banerjee, and S. S. Mitra, "Raman scattering in optical fibers," *J. Raman Spectrosc.*, vol. 11, no. 5, pp. 416–423, Oct. 1981.

[122] S. Claramunt, A. Varea, D. López-Díaz, M. M. Velázquez, A. Cornet, and A. Cirera, "The Importance of Interbands on the Interpretation of the Raman Spectrum of Graphene Oxide," *J. Phys. Chem. C*, vol. 119, no. 18, pp. 10123–10129, May 2015.

[123] A. A. Dubale, W.-N. Su, A. G. Tamirat, C.-J. Pan, B. A. Aragaw, H.-M. Chen, C.-H. Chen, and B.-J. Hwang, "The synergetic effect of graphene on Cu2O nanowire arrays as a highly efficient hydrogen evolution photocathode in water splitting," *J. Mater. Chem. A*, vol. 2, no. 43, pp. 18383–18397, 2014.

[124] T. D. T. Dang, N. Anh Tuan, P. Khoa Nhat Thanh, T. An Thu Thi, D. Tin Chanh Duc, and M. Chien, "Modification of silicon nitride surfaces with GOPES and APTES for antibody immobilization: computational and experimental studies," *Adv. Nat. Sci. Nanosci. Nanotechnol.*, vol. 6, no. 4, p. 45006, 2015.

[125] Q. Ye, T. Gao, F. Wan, B. Yu, X. Pei, F. Zhou, and Q. Xue, "Grafting poly(ionic liquid) brushes for anti-bacterial and anti-biofouling applications," *J. Mater. Chem.*, vol. 22, no. 26, pp. 13123–13131, 2012.

[126] S.-P. Lin, T.-Y. Chi, T.-Y. Lai, and M.-C. Liu, "Investigation into the Effect of Varied Functional Biointerfaces on Silicon Nanowire MOSFETs," *Sensors* , vol. 12, no. 12. 2012.

[127] E. Ayrat, M. Dimiev; Siegfied, *Graphene Oxide: Fundamentals and Applications*. 2016.

[128] D. Berman, A. Erdemir, A. V Zinovev, and A. V Sumant, "Nanoscale friction properties of graphene and graphene oxide," *Diam. Relat. Mater.*, vol. 54, pp. 91–96, Apr. 2015.

[129] V. Singh and S. Krishnan, "An electrochemical mass sensor for diagnosing diabetes in human serum," *Analyst*, vol. 139, no. 4, pp. 724–728, 2014.

[130] H. S. Dong and S. J. Qi, "Realising the potential of graphene-based materials for biosurfaces – A future perspective," *Biosurface and Biotribology*, vol. 1, no. 4, pp. 229–248, 2015.

[131] P. Montes-Navajas, N. G. Asenjo, R. Santamaría, R. Menéndez, A. Corma, and H. García, "Surface Area Measurement of Graphene Oxide in Aqueous Solutions," *Langmuir*, vol. 29, no. 44, pp. 13443–13448, Nov. 2013.

[132] P. Kesharwani, S. Banerjee, U. Gupta, M. C. I. Mohd Amin, S. Padhye, F. H. Sarkar, and A. K. Iyer, "PAMAM dendrimers as promising nanocarriers for RNAi therapeutics," *Mater. Today*, vol. 18, no. 10, pp. 565–572, 2015.

[133] J. Yang, S. Cao, J. Li, J. Xin, X. Chen, W. Wu, F. Xu, and J. Li, "Staged self-assembly of PAMAM dendrimers into macroscopic aggregates with a microribbon structure similar to that of amelogenin," *Soft Matter*, vol. 9, no. 31, pp. 7553–7559, 2013.

[134] T. V. Long and F. R. Huege, “The laser-Raman spectrum of ferrocene,” *Chem. Commun.*, no. 20, p. 1239b–1241, 1968.

[135] C. M. González-Henríquez, C. A. Terraza, and M. Sarabia, “Theoretical and Experimental Vibrational Spectroscopic Investigation of Two R1R2-Diphenylsilyl-Containing Monomers and Their Optically Active Derivative Polymer,” *J. Phys. Chem. A*, vol. 118, no. 7, pp. 1175–1184, Feb. 2014.

[136] Ottman Belaidi, T. Bouchaour, and U. Maschke, “Molecular Structure and Vibrational Spectra of 2-Ethylhexyl Acrylate by Density Functional Theory Calculations,” *Org. Chem. Int.*, vol. 2013, p. 14, 2013.

[137] S. L. Sewell, R. D. Rutledge, and D. W. Wright, “Versatile biomimetic dendrimer templates used in the formation of TiO2 and GeO2,” *Dalt. Trans.*, no. 29, pp. 3857–3865, 2008.

[138] O. Arotiba, J. Owino, E. Songa, N. Hendricks, T. Waryo, N. Jahed, P. Baker, and E. Iwuoha, “An Electrochemical DNA Biosensor Developed on a Nanocomposite Platform of Gold and Poly(propyleneimine) Dendrimer,” *Sensors* , vol. 8, no. 11. 2008.

[139] P. Wang, G. Brambilla, M. Ding, Y. Semenova, Q. Wu, and G. Farrell, “High-sensitivity, evanescent field refractometric sensor based on a tapered, multimode fiber interference,” *Opt. Lett.*, vol. 36, no. 12, pp. 2233–2235, 2011.

[140] H. Latifi, M. I. Zibaii, S. M. Hosseini, and P. Jorge, “Nonadiabatic tapered optical fiber for biosensor applications,” *Photonic Sensors*, vol. 2, no. 4, pp. 340–356, Oct. 2012.

[141] W. R. Wong, S. D. Sekaran, F. R. Mahamd Adikan, and P. Berini, “Detection of dengue NS1 antigen using long-range surface plasmon waveguides.,” *Biosens. Bioelectron.*, vol. 78, pp. 132–9, Apr. 2016.

[142] W. R. Wong, S. D. Sekaran, F. R. Mahamd Adikan, and P. Berini, “Detection of dengue NS1 antigen using long-range surface plasmon waveguides,” *Biosens. Bioelectron.*, vol. 78, pp. 132–139, Apr. 2016.